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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Ulrich MARTIN, *et al.*

Application Serial No. 09/013,871

Filed: January 27, 1998

Group Art Unit: 1644

Examiner: Gambel, P.

Attorney's Docket No: 05882.0002.PCUS00

For: **ANTI-SELECTIN ANTIBODIES FOR PREVENTION OF MULTIPLE ORGAN FAILURE AFTER POLYTRAUMA AND FOR PREVENTION OF ACUTE ORGAN DAMAGE AFTER EXTRACORPOREAL BLOOD CIRCULATION**

APPEAL BRIEF PURSUANT TO 37 CFR 1.192

BOX AF
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

This is an appeal of the Examiner's Final rejection of pending Claims 22, 23, 27, and 29-45 submitted on or before the extended due date of May 18, 2001. Appellant hereby appeals from the Final Rejection of April 18, 2000. Submitted herewith are three copies of Appellant's brief on appeal, together with the requisite fee.

(1) Real Party of Interest

Protein Design Labs, Inc. and Scil Biomedicals GmbH are the real parties of interest in the application at the time that the Brief is being filed.

(2) **Related Appeals and Interference**

There are no related appeals or interference known to appellant, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) **Status of Claims**

Claims 1-21, 24-26, and 28 have been cancelled.

Claims 22, 23, 27, and 29-45 were rejected. Claims 22, 23, 27, and 29-45 are present in the application. Claims 22, 23, 27, and 29-45 are on appeal.

(4) **Status of Amendments**

There has been no amendment filed subsequent to final rejection dated April 18, 2000.

(5) **Summary of the Invention**

Claim 22 is directed to a method for prevention of multiorgan failure after a polytraumatic event, comprising administrating an amount of anti-L-selectin antibody in a pharmaceutically acceptable carrier to said patient, in an amount sufficient to prevent said multiorgan failure. Claim 22 is supported by page 5, lines 15-19; and, page 7, line 15.

Claims 23 and 27 depend on Claim 22. Claim 23 recites that the anti-L-selectin antibody is humanized. Claim 23 is supported by page 15, lines 9-10. Claim 27 recites that the anti-L-selectin antibody is Dreg 55 or HuDreg 55. Claim 27 is supported by page 11, line 19 to page 12, line 1; and, page 13, lines 19-20.

Claim 29 is directed to method for treating a patient who has suffered a severe polytraumatic event comprising administering to said patient a therapeutically effective amount of an anti-L-selectin antibody in a pharmaceutically acceptable carrier to said patient. Claim 29 is supported by page 5, lines 15-19; and, page 7, line 15.

Claims 30-40 depend on Claim 29. Claim 30 recites that the method comprises administering a dose of from 1.0 to 10 mg/kg of body weight of said patient to said patient, from 1 to 5 times after suffering said severe polytraumatic event. Claim 30 is supported by page 10,

lines 1-3. Claim 31 recites that the method comprises administering a first dose of said anti-L-secretin antibody from 0.5 to 8 hours after said severe polytraumatic event. Claim 31 is supported by page 10, lines 3-5. Claim 32 recites that the method comprises administering said first dose from 0.5 to 4 hours after said severe polytraumatic event. Claim 32 is supported by page 10, lines 3-5. Claim 33 recites that the method comprises administering doses of said anti-L-selectin antibody at intervals of from 6 to 72 hours. Claim 33 is supported by page 10, lines 5-6. Claim 34 recites that the method comprises administering doses of said anti-L-selectin at intervals of from 6 to 36 hours. Claim 34 is supported by page 10, lines 5-6. Claim 35 recites that the method comprises administering said anti-L-selectin antibody up to 10 days after said severe polytraumatic event. Claim 35 is supported by page 10, lines 9-11. Claim 36 recites that the method comprises determining concentration and timing of administration of does of said anti-L-selectin antibody by determining concentrations of anti-L-selectin antibody in serum or plasma of said patient 6-24 hours after administration of a prior dose of said anti-L-selectin antibody. Claim 36 is supported by page 10, lines 12-14. Claim 37 recites that a dose of up to 10 mg/kg is administered to a patient in whose serum or plasma concentration of anti-L-selectin antibody is less than 10 μg/ml. Claim 37 is supported by page 10, lines 1-2 and 12-16. Claim 38 recites that a dose which is half of a prior dose of anti-L-selectin antibody is administered to a patient in whose serum or plasma concentration of anti-L-selectin antibody is between 10 μg/ml and 50 μg/ml. Claim 38 is supported by page 10, lines 16-19. Claim 39 recites that the anti-L-selectin antibody is a humanized antibody. Claim 39 is supported by page 15, lines 9-10. Claim 40 recites that the humanized antibody is HuDreg55 or HuDreg200, wherein antibody HuDreg55 comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:2 and a heavy chain variable region having a amino acid sequence as set forth in SEQ ID NO:4, and antibody HuDreg200 comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:5 and a heavy chain variable region having a amino acid sequence as set forth in SEQ ID NO:6. Claim 40 is supported by page 11, line 19 to page 12, line 2.

Claim 41 is directed to a method for preventing acute organ damage associated with

extracorporeal circulation of a patient's blood through a heart-lung machine, comprising contacting said patient's blood when it is circulating through said heart-lung machine with a pharmaceutical composition with an anti-L-antibody in a pharmaceutical acceptable carrier 1-30 minutes prior to terminating extracorporeal circulation through said heart-lung machine, at a dose of 1.0-10 mg/kg of body weight of said patient. Claim 41 is supported by page 7, lines 2-7.

Claims 42-45 depend on Claim 40. Claim 42 recites that said dose contains from 2.0 - 4.0 mg/kg of body weight of said patient. Claim 42 is supported by page 7, line 7. Claim 43 recites that said anti-L-selectin antibody is a humanized monoclonal antibody. Claim 43 is supported by page 15, lines 9-10. Claim 44 recites that said anti-L-selectin antibody is HuDreg200 or HuDreg55, wherein antibody HuDreg55 comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:2 and a heavy chain variable region having a amino acid sequence as set forth in SEQ ID NO:4, and antibody HuDreg200 comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:5 and a heavy chain variable region having a amino acid sequence as set forth in SEQ ID NO:6. Claim 44 is supported by page 11, line 19 to page 12, line 2. Claim 45 recites that administering 1-3 doses of anti-L-selectin antibody to said patient, each of said doses containing 1-4 mg/kg of body weight of said patient. Claim 45 is supported by page 7, lines 9-11.

(6) Issues

There are five issues in question:

(a). Whether the terms "Dreg55", "HuDreg55", and "HuDreg200", in Claims 27, 40, and 44, are indefinite such that these claims are rendered unpatentable under 35 U.S.C. § 112, second paragraph.

(b). Whether Claims 22, 23, 27, 29-33, 39, and 41-45 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by Co.

(c). Whether Claims 29-33, 39, and 41-45 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by Lefer.

(d). Whether Claims 29-33, 39, and 41-45 are unpatentable under 35 U.S.C. § 102(e) as being anticipated by Tedder, *et al.*

(e). Whether Claims 22, 23, 27, and 29-45 are unpatentable under 35 U.S.C. § 103(a) as being rendered obvious over Co and/or Lefer and/or Tedder, *et al.* and/or Buerke, *et al.* in view of Butcher, *et al.*, Springer, *et al.*, Moat, *et al.*, and Finn, *et al.*

(7) Grouping of Claims

Appellants assert that the claims are noteworthy patentable and thus do not stand or fall together. The reason as to why Appellants consider the rejected claims to be separately patentable is because the claims are directed to different methods of preventive or therapeutic treatments. Reasons as to why Appellants consider the rejected claims to be separately patentable are included in paragraph (8) below in the arguments relating to the individual rejections. Briefly, Claims 22, 23, and 27 are directed to a method for prevention of multiorgan failure after a polytraumatic event. Claims 29-40 are directed to method for treating a patient who has suffered a severe polytraumatic event. Claims 41-45 are directed to a method for preventing acute organ damage associated with extracorporeal circulation of a patient's blood through a heart-lung machine.

(8) Argument

(a). Whether the terms "Dreg55", "HuDreg55", and "HuDreg200", in Claims 27, 40, and 44, are indefinite such that these claims are rendered unpatentable under 35 U.S.C. § 112, second paragraph.

In the final office action, Claims 27, 40, and 44 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The essential inquiry pertaining to whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

If the scope of the invention sought to be patented cannot be determined from the language of the claims with a reasonable degree of certainty, a rejection of the claims under 35 U.S.C. 112, second paragraph is appropriate. *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973).

When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989).

The Examiner states that:

> Claims 27, 40 and 44 are indefinite in the recitation of "Dreg 55 or HuDreg 55, HuDreg 200" because their characteristics are not known. The use of "these terms" as the sole means of identifying the claimed antibodies renders the claim indefinite because "these terms" are merely laboratory designations which do not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct cell lines or hybridomas. Applicant should amend the claims to include the SEQ ID NOS. to clearly identify the biological species. (page 2, lines 22-26).

Appellant submit that the Examiner is erroneous in alleging that the characteristics of Dreg55, HuDreg55, and HuDreg200 are unknown.

Based on the content of the present application disclosure, the teachings of the prior art, the claims interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made, it is clear that the terms "Dreg55", "HuDreg55", and "HuDreg200" define specific antibody molecules and are **not** merely laboratory designations that do not clearly define the claimed product. The content of the present application and the teachings of the prior art clearly teach that "Dreg55" is a specific mouse monoclonal antibody (page 17, lines 15-16; Kishimoto, *et al.*, *Proc. Natl. Acad. Sci. USA*, 87:2244-8, 1990),

"HuDreg55" is a specific humanized monoclonal antibody (page 16, lines 12-15), and "HuDreg200" is a specific mouse monoclonal antibody (page 11, line 19 to page 12, line1; WO 94/12215; WO 95/15181; Buerke, *et al., J. Pharmacol. Exp. Ther.* 271:134-42, 1994). Based on the content of the present application and teachings of the prior art, one of ordinary skill in the pertinent art at the time the invention was made, would clearly interpret the terms "Dreg55", "HuDreg55", and "HuDreg200" define specific antibody molecules, and would be interpreted as any other molecules or matter.

Therefore, the terms "Dreg55", "HuDreg55", and "HuDreg200" are labels known and accepted in the pertinent art to define specific antibody molecules.

Therefore, the Examiner erred in rejecting Claims 27, 40, and 44 under 35 U.S.C. §112, second paragraph, because the terms "Dreg55", "HuDreg55", and "HuDreg200" with a reasonable degree of clarity and particularity define specific antibody molecules.

(c) Whether Claims 22, 23, 27, 29-33, 39, and 41-45 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by Co.

In the final office action, Claims 22, 23, 27, 29-33, 39, and 41-45 were rejected under 35 U.S.C. §102(b) as being anticipated by Co (WO 94/12215).

The legal standard for a novelty rejection is that a claim is anticipated only if each and every element as set forth in the claim is found, is either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). Anticipation is a question of fact. *In re Lee*, 31 U.S.P.Q.2d 1105, 1108 (Bd. Pat. App. & Inter. 1993) (expanded Board) (citing In re King, 801 F.2d 324, 231 U.S.P.Q. 136 (Fed. Cir. 1986).

A reference anticipates a claim if it discloses the claimed invention "such that a skilled artisan could take its teachings in combination with his own knowledge of a particular art and be in possession of the invention." *In re LeGrice*, 301 F.2d 929, 936, 133 U.S.P.Q. 365, 372

(C.C.P.A. 1962).; In re Donohue, 766 F.2d 531, 533, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985). A § 102(b) reference "must sufficiently describe the claimed invention to have placed it placed the public in possession of it." *Paperless Accounting, Inc. v. Bay Area Rapid Transit System*, 231 U.S.P.Q. 649, 653 (Fed. Cir. 1986) (citing 226 U.S.P.Q. at 621). The court observed in *Donohue* that "even it the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." 226 U.S.P.Q. at 621 (citing *In re Borst*, 345 F.2d 851, 855, 145 U.S.P.Q. 554, 557 (C.C.P.A. 1965).

Co discloses the following:

> The antibodies of the present invention will typically find use in the treatment of disease conditions with an inflammatory component, especially those which are mediated by neutrophils or T cells. A preferred application is the therapeutic and prophylactic treatment of ischemia-reperfusion injury caused by myocardial infarction, cerebral ischemic event (e.g., stroke), renal, hepatic or splenal infarction, brain surgery, shock, cardiac surgery (e.g., coronary artery bypass), elective angioplasty, and the like. Other preferred applications are the treatment of sepsis, adult respiration distress syndrome, and multiple organ failure. The antibodies will find use in treating injury due to trauma, burns, frostbite or damage to the spinal cord. They will also find use in treating autoimmune diseases including by way of example and not limitation, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type I diabetes and uveitis, in treating inflammatory diseases of the skin such as psoriasis, and in treating meningitis and encephalitis. Other typical applications are the prevention and treatment of organ transplant rejection and graft-versus-host disease. (page 29, lines 15-35).

The Examiner erred in rejecting Claims 22, 23, and 27 as being anticipated by Co, because Co does not anticipate a method for prevention of multiorgan failure after a polytraumatic event. Co discloses prevention and treatment of a variety of injuries, syndromes, disorders and diseases; however, none of these is a polytraumatic event. A polytraumatic event is an event that results in a simultaneously acquired injury of at least two or more organ systems. Injuries resulting from a polytraumatic event are immediately life threatening due to the combination of the injured organ systems or due to the fact that one of the at least two injuries is per se life threatening. For example, both a femur fracture or a lung contusion may not be life threatening as separate single injuries, but in combination such a polytraumatic injury holds a

20% mortality risk. Appellants respectfully point out that the Examiner admits that "it is acknowledged that the prior art does not explicitly disclose polytraumatic events" (page 7, line 18). Co neither expresses nor inherently describes a polytraumatic event. Co merely discloses "treating injuries due to trauma" (page 29, lines 26-27) but fails to describe methods for treating injuries arising from "a polytraumatic event". The ischemia-reperfusion injury disclosed by Co does not anticipate "a polytraumatic event" of Claims 22, 23, and 27. In fact, Co discloses that the ischemia-reperfusion injury can be "caused by . . . multiple organ failure" (page 29, lines 20-26), whereas the claimed method encompasses a method for prevention of multiorgan failure *after* a polytraumatic event. In other words, Co discloses a method of prophylactic treatment of ischemia-reperfusion injury *after* multiple organ failure, while the claimed method is a prophylactic treatment *prior* to organ failure. Since Co neither expresses nor inherently describes a polytraumatic event, each and every element set forth in Claims 22, 23, and 27 is not found in Co; therefore, the Examiner erred in alleging the anticipation of Claims 22, 23, and 27 by Co.

The Examiner erred in rejecting Claims 29-33 and 39 as being anticipated by Co, because Co does not anticipate a method for treating a patient who has suffered a severe polytraumatic event. As discussed above, Co discloses prevention and treatment of a variety of injuries, syndromes, disorders and diseases; however, none of these is a polytraumatic event. Since Co neither expresses nor inherently describes a polytraumatic event, each and every element set forth in Claims 29-33 and 39 is not found in Co; therefore, the Examiner erred in alleging the anticipation of Claims 29-33 and 39 by Co.

The Examiner erred in rejecting Claims 41-45 as being anticipated by Co. Co does not anticipate Claims 41-45, because Co does not anticipate a method for preventing acute organ damage associated with extracorporeal circulation of a patient's blood through a heart lung machine. Co discloses the prophylactic treatment of ischemia-reperfusion injury; however, does not disclose acute organ damage associated with extracorporeal circulation of a patient's blood through a heart lung machine. Since Co neither expresses nor inherently describes (1) acute organ damage associated with extracorporeal circulation, or (2) extracorporeal circulation of a patient's blood through a heart lung machine, each and every element set forth in Claims 41-45 is

not found in Co; therefore, the Examiner erred in alleging the anticipation of Claims 41-45 by Co.

For the reasons stated above, the Examiner erred in rejecting Claims 22, 23, 27, 29-33, and 41-45 under 35 U.S.C. §102(b) as being anticipated by Co.

(c). Whether Claims 29-33, 39, and 41-45 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by Lefer.

In the final office action, Claims 29-33, 39, and 41-45 were rejected under 35 U.S.C. §102(b) as being anticipated by Lefer (WO 95/95181).

The legal standard is identical to that outlined for the 35 U.S.C. §102(b) rejection over Co.

Lefer discloses the following:

> The invention provides methods for reperfusion therapy using the therapeutic agents and pharmaceutical conditions discusses *supra*. The methods are particularly useful for therapeutic and prophylactic treatment of ischemia-reprefusion injury caused by, for example, myocardial infarction, cardiac surgery, such as coronary artery bypass or elective angioplasty, cerebral ischemic event (*e.g.*, a stroke or brain surgery), renal, splenic or hepatic ischemic events, shock, (*e.g.*, hemorrhagic-shock-induced gastric musocal injury), and the like. (page 21, lines 23-32).

The Examiner erred in rejecting Claims 29-33 and 39 as being anticipated by Lefer, because Lefer does not anticipate a method for treating a patient who has suffered a severe polytraumatic event but merely discloses prevention or treatment of reperfusion injury in a patient and treating patients suffering from myocardial ischemia. As pointed out earlier, the Examiner admits that "the prior art does not explicitly disclose polytraumatic events" (page 7, line 18). Lefer neither expresses nor inherently describes a polytraumatic event. Lefer does not even disclose a single trauma event. The ischemia-reperfusion injury disclosed by Lefer is not "a polytraumatic event" of Claims 29-33 and 39. Since Lefer neither expresses nor inherently describes a polytraumatic event, each and every element set forth in Claims 29-33 and 39 is not

found in Lefer; therefore, the Examiner erred in alleging the anticipation of Claims 29-33 and 39 by Lefer.

The Examiner erred in rejecting Claims 41-45 as being anticipated by Lefer, because Lefer does not anticipate a method for preventing acute organ damage associated with extracorporeal circulation of a patient's blood through a heart lung machine. Lefer discloses prevention or treatment of reperfusion injury in a patient and treating patients suffering from myocardial ischemia, but does not disclose acute organ damage associated with extracorporeal circulation of a patient's blood through a heart lung machine. Since Lefer neither expresses nor inherently describes (1) acute organ damage associated with extracorporeal circulation, or (2) extracorporeal circulation of a patient's blood through a heart lung machine, each and every element set forth in Claims 41-45 is not found in Lefer; therefore, the Examiner erred in alleging the anticipation of Claims 41-45 by Lefer.

For the reasons stated above, the Examiner erred in rejecting Claims 29-33, 39, and 41-45 under 35 U.S.C. §102(b) as being anticipated by Lefer.

(d). Whether Claims 29-33, 39, and 41-45 are unpatentable under 35 U.S.C. § 102(e) as being anticipated by Tedder, *et al.*

In the final office action, Claims 29-33, 39, and 41-45 were rejected under 35 U.S.C. §102(b) as being anticipated by Tedder, *et al.* (U.S. Patent No. 5,679,346).

The legal standard is identical to that outlined for 35 U.S.C. §102(b) rejection over Co.

Tedder, *et al.* discloses the following:

> In another aspect, the invention features a method of treating a human patient suffering from a lymphocyte-mobilizing condition which involves administering a therapeutic amount of an antagonist to LAM-1 in a non-toxic pharmaceutical carrier substance. In preferred embodiments of the method the patient is suffering from tissue damage, an autoimmune disorder, or cancer, or the patient is an organ or tissue transplant recipient. (col. 2, lines 3-30).
>
> Neutrophil-mediated inflammation is involved in a number of human clinical manifestations, including the adult respiratory distress syndrome, multi-organ failure and reperfusion injury. . . . [I]t is likely that the use of anti-LAM1-3 will block lymphocyte entry into sites of inflammation or tissue injury. Such activity will be useful for

preventing kidney or other organ transplant rejection which is mediated by lymphocytes. (col. 6, lines 53-65).

The Examiner erred in rejecting Claims 29-33 and 39 as being anticipated by Tedder, *et al.*, because Tedder, *et al.* does not anticipate a method for treating a patient who has suffered a severe polytraumatic event. As pointed out earlier, the Examiner admits that "the prior art does not explicitly disclose polytraumatic events" (page 7, line 18). Tedder, *et al.* merely discloses a method of treating a human patient suffering from a lymphocyte-mobilizing condition, such as from tissue damage, an autoimmune discorder, or cancer, or from an organ or tissue transplant. Tedder, et al. also discloses "human clinical manifestations, including the adult respiratory distress syndrome, multi-organ failure and reperfusion injury". None of the diseases or conditions disclosed by Tedder, et al. is a polytraumatic event.

Since Tedder, *et al.* neither expresses nor inherently describes a polytraumatic event, each and every element set forth in Claims 29-33 and 39 is not found in Tedder, *et al.*; therefore, the Examiner erred in alleging the anticipation of Claims 29-33 and 39 by Tedder, *et al.*

The Examiner erred in rejecting Claims 41-45 as being anticipated by Tedder, *et al.*, because Tedder, *et al.* does not anticipate a method for preventing acute organ damage associated with extracorporeal circulation of a patient's blood through a heart lung machine. Tedder, *et al.* discloses prevention or treatment of reperfusion injury in a patient, but does not disclose acute organ damage associated with extracorporeal circulation of a patient's blood through a heart lung machine. Since Tedder, *et al.* neither expresses nor inherently describes (1) acute organ damage associated with extracorporeal circulation, or (2) extracorporeal circulation of a patient's blood through a heart lung machine, each and every element set forth in Claims 41-45 is not found in Tedder, *et al.*; therefore, the Examiner erred in alleging the anticipation of Claims 41-45 by Tedder, *et al.*

For the reasons stated above, the Examiner erred in rejecting Claims 29-33, 39, and 41-45 under 35 U.S.C. §102(e) as being anticipated by Tedder, *et al.*

(e). Whether Claims 22, 23, 27, and 29-45 are unpatentable under 35 U.S.C. § 103(a) as being rendered obvious over Co and/or Lefer and/or Tedder, *et al.* and/or Buerke, *et al.* in view of Butcher, *et al.*, Springer, *et al.*, Moat, *et al.*, and Finn, *et al.*

In the final office action, Claims 22, 23, 27, and 29-45 were rejected under 35 U.S.C. §103 as being rendered obvious by Co and/or Lefer and/or Tedder, *et al.* and/or Buerke, *et al.* (*J. Pharmacol. Exp. Ther.*, 271:134-42, 1994) in view of Butcher, *et al.* (U.S. Patent No. 5,316,913), Springer, *et al.* (U.S. Patent No. 5,460,945), Moat, *et al.* (*Ann. Thorac. Surg.*, 56:1509-14, 1993), and Finn, *et al.* (*Perfusion*, 8:39-48, 1993).

Under 35 U.S.C. §103(a) rejection is proper only when the subject matter of the claims as a whole would have been obvious at the time the invention was made to one of ordinary skill in the art to which the subject matter pertains. Determination of obviousness under 35 U.S.C. §103 involves four factual inquires as follows:

(A) determining the scope of and content of the prior art;

(B) ascertaining the differences between the prior art and the claims in issue;

(C) resolving the level of ordinary skill in the pertinent art; and

(D) evaluation evidence of secondary considerations.

See Graham v John Deere Co., 383 U.S. 1, 148 U.S.P.Q. 459 (1966).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *in re Jones*, 958 F2d 347, 21 U.S.P.Q.2d 1941 (Fed Cir. 1992). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q. 2d 1430 (Fed. Cir. 1990).

It is essential to consider all elements of the claimed invention; it is impermissible to compare the prior art with what the viewer interprets the "gist" of the invention to be. *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). It is impermissible to

ignore advantages, properties utilities, and unexpected results flowing form the claimed invention; they are part of the invention as a whole. *In re Chupp*, 816 F.2d 643, 2 U.S.P.Q.2d 1437 (Fed. Cir. 1987). When the components of a new composition are deemed to be structurally similar to components of know compositions, but a new use is discovered, the new use of the composition is patentable. *See In re Shetty*, 566 F.2d 81, 86, 195 USPQ 753, 756 (C.C.P.A. 1977) (adjacent homolog held "structurally similarly" to prior art compound, requiring evidence of actual difference of properties to compound claim, but not for method claims); and *In re Ruschig*, 343 F.2d 965, 977, 145 U.S.P.Q. 274, 285 (C.C.P.A. 1965) ("What is important is the fact that the utility *discovered by appellants* is not disclosed in the prior art." (emphasis in original)). Thus in evaluating the patentability of the applicants' method claims, it is not pertinent whether the compositions themselves are known or new or unobvious. *See, e.g., In re May*, 574 F.2d 1082, 1093, 197 U.S.P.Q. 601 (C.C.P.A. 1978) (claims to use non-addictive analgesics for May's compounds held unobvious from the known use of the prior art compounds as addictive analgesics, in view of the unpredictable nature of this property).

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

Conclusions based on hindsight reasoning are improper, unless they take into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and do not include knowledge gleaned only from applicant's disclosure. *In re Laughlin*, 443 F.2d 1392, 1395, 170 U.S.P.Q. 209, 212 (C.C.P.A. 1971). It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983).

Buerke, *et al.* discloses that a humanized anti-L-selectin monocolonal antibody, HuDreg200, appears to be an effective means of preserving the ischemic myocardium from reperfusion injury based on a feline model of myocardial ischemia followed by reperfusion.

Butcher, *et al.* discloses a method for determining neutrophil activation in a mammalian host by detecting the presence of shed LECAM-1, a neutrophil epitope, in the blood by using a monocolonal antibody which binds to a common epitope of lymphocyte and neutrophil LECAM-1.

Springer, *et al.* discloses that selectins, which can competitively block binding of neutrophils or other leukocytes, can have use therapeutically in diseases or disorders involving extravasation of leukocytes.

Moat, *et al.* discloses that there is complement activation, changes in adhesion molecule expression and interleukin-8 generation in a simulated extracorporeal circulation.

Finn, *et al.* discloses that all expression of L-selectin is lost in children undergoing cardiopulmonary bypass surgery.

The Examiner has not established a *prima facie* case of obviousness for Claims 22, 23, 27, and 29-45 based on the cited references, because (1) the references do not disclose all the claim limitations, (2) there is no reasonable expectation of success in using the claimed method, (3) there are new advantages and unexpected results from the use of anti-L-selectin antibodies in the claimed methods, and (4) the Examiner erred in relying on hindsight reasoning to conclude the claimed method is obvious over the prior art.

(1) The references do not disclose all the claim limitations.

Appellants respectfully point out that the Examiner admits that "it is acknowledged that the prior art does not explicitly disclose polytraumatic events" (page 7, line 18). As explained earlier, polytrauma is very distinct from ischemia reperfusion or mere trauma in that the complications and dangers of polytrauma are not merely additive of the combined injuries to two or more organ systems, but the combination further increases the immediate life threatening danger.

In regards to Claims 22, 23, and 27, none of the references teach or suggest a method for prevention of multiorgan failure after a polytraumatic event. None of the references teach or suggest the claim limitation of "multiorgan failure after a polytraumatic event".

In regards to Claims 29-40, none of the references teach or suggest a method for treating a patient who has suffered a severe polytraumatic event. None of the references teach or suggest the claim limitation of "a severe polytraumatic event".

In regards to Claims 41-45, none of the references teach or suggest a method for preventing acute organ damage associated with extracorporeal circulation of a patient's blood through a heart lung machine. None of the references teach or suggest the claim limitation of "extracorporeal circulation of a patient's blood through a heart lung machine".

Since the all the claim limitations of each of Claims 22, 23, 27, and 29-41 are not taught or suggested by the references cited by the Examiner, Appellants respectfully contend that the Examiner has not met the *prima facie* burden for establishing a prima facie case of obviousness.

(2) There is no reasonable expectation of success in using the claimed method.

Appellants contend that using the methods of Co, Lefer, Tedder, *et al.*, and the other references, there would have been no reasonable expectation of success of (1) prevention of multiorgan failure after a polytraumatic event, (2) treating a patient who has suffered a severe polytraumatic event, and/or (3) preventing acute organ damage associated with extracorporeal circulation of a patient's blood through a heart lung machine. While Co and Lefer disclose the use of humanized Dreg55 and Dreg200, however, Co and/or Lefer, either alone or combined with the other references, do not teach or suggest that these specific antibodies, or any other antibodies, are capable of either prevention of multiorgan failure or for treatment following a polytraumatic event. There is no reasonable basis to support that specific antibodies useful for treating ischemia-reperfusion (Co and Lefer only provide working examples of ischemia-reperfusion treatment) would be useful for treating of conditions following a polytraumatic event. As explained earlier, ischemia reperfusion is very distinct from polytrauma in that the complications and dangers of polytrauma are not merely additive of the combined injuries to two or more organ systems, but the combination further increases the immediate life threatening danger. In fact, there is teaching away from the claimed methods, where a humanized leucointegrin antibody failed in treating trauma-induced haemorrhagic shock originating from

blunt or penetrating injury (*see* "LeukArrest fails in haemorrhagic shock", *SCRIP* 2448:19, 1999; a copy of which is attached to the Response to Office Action dated February 4, 2000).

Since, based on the cited references, there is no reasonable expectation of success that the method of Claims 22, 23, 27, and 29-41 would be effective, Appellants respectfully contend that the Examiner has not met the *prima facie* burden for establishing a prima facie case of obviousness. Therefore, the Examiner has erred in rejecting these claims under 35 U.S.C. §103.

(3) There are new advantages and unexpected results from the use of anti-L-selectin antibodies in the claimed methods.

The Examiner has erred in ignoring the new advantages and unexpected results taught in the specification.

The specification states:

> It has *surprisingly* turned out that it is possible to prevent multiple organ failure when anti-selectin antibodies, especially anti-L-selectin antibodies, are administered very soon after the polytrauma. This is also *surprising* because there is no acute symptom at this very early stage and there would therefore have been no reason to administer such a dose as a preventive measure.
>
> It also *surprisingly* turned out that anti-slectin antibodies in doses of 1.0 - 10 mg/kg, prefereably of 2 - 4 mg/kg, administered one to five times, preferably once or twice after the polytrauma event can advantageouosly be used . . . . (page 9, line 16 to page 10, line 3; emphasis added).

None of the stated results and methods were either known or expected at the time of invention. One skilled in the art would not have expected such results. The methods of Claims 22, 23, and 27 provide a new advantage in that it is possible to prevent multiorgan failure to administer anti-selectin antibodies as a preventive measure, which was neither known nor considered prior to this invention.

Since, based on the cited references, it is clear that the results of this invention are unexpected and the claimed methods demonstrate a new use of the anti-selectin antibodies. Therefore, the Examiner has erred in rejecting these claims under 35 U.S.C. §103.

(4) The Examiner erred in relying on hindsight reasoning to conclude the claimed method is obvious over the prior art.

The Examiner alleges that: "While it is acknowledged that the prior art does not explicitly disclose polytraumatic events; it is *clear* that the prior art methods encompass polytraumatic events by teaching inhibiting multi organ failure and hemorrhagic shock with L-selectin antibodies." (page 7, lines 18-20; emphasis added). The Examiner alleges that method encompassing polytraumatic events are "clear"; however, Appellants respectfully point out that the Examiner provides no reasoning as to why it is "clear" that the prior art methods encompass polytraumatic events. The Examiner alleges that teaching "multi organ failure" and "hemorrhagic shock" are polytraumatic events; however, while "multi organ failure" and "hemorrhagic shock" *may* result from a polytraumatic event, but they do not *necessarily* result from a polytraumatic event. Therefore, absent hindsight reconstruction, one skilled in the art would not necessarily conclude that the prior art methods encompass polytraumatic events merely due to the allusion to multi organ failure and hemorrhagic shock.

The Examiner also alleges that: "the ordinary artisan would have expected to reduce the probability of organ failure after a polytraumatic event, given the teachings of the prior art, including Methods of Use/Therapeutic Methods, as taught by Co and Lefer." (page 8, lines 11-13). However, the "Method of Use" section of Co (pages 29-36) and the "Therapeutic Methods" section of Lefer (pages 21-26) do not suggest a method of prevention of multiorgan failure after a polytraumatic event. Appellants respectfully point out that the Examiner provides no reasoning as to why the "Methods of Use" and "Therapeutic Methods" sections of Co and Lefer, respectively, would suggest the claimed methods. In fact, Co discloses that the ischemia-reperfusion injury can be "caused by . . . multiple organ failure" (page 29, lines 20-26). That Co discloses treating a condition *after* multiple organ failure actually teaches away from treating a patient *before* multiple organ failure to prevent multiorgan failure (which occurs *after* a polytraumatic event, but *before* the ischemia-reperfusion injury disclosed by Co). Therefore, absent hindsight reconstruction, one skilled in the art would not necessarily conclude that the prior art methods encompass a method of prevention of multiorgan failure after a polytraumatic event.

(5) Conclusion.

For the reasons explained above, the cited references, either combined or alone, do not teach or suggest Claims 22, 23, 27, and 29-41. Therefore, the Examiner has erred in rejecting these claims under 35 U.S.C. §103.

(9) Appendix

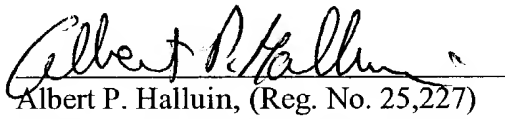
An appendix containing a copy of the claims involved in the appeal is attached herewith.

(10) Conclusion

For the reasons stated above, the Examiner's rejection of Claims 22, 23, 27, and 29-45 is erroneous. The Honorable Board is respectfully requested to reverse the Examiner's rejection of all claims on appeal and remand the application to the Examiner for allowance.

Respectfully submitted

Date: May 18, 2001



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Appendix: Pending Claims on Appeal

22. A method for prevention of multiorgan failure after a polytraumatic event, comprising administering an amount of an anti-L-selectin antibody in a pharmaceutically acceptable carrier to said patient, in the amount sufficient to prevent said multiorgan failure.

23. The method of claim 22, wherein the anti-L-selectin antibody is humanized.

27. The method of claim 22, wherein the anti-L-selectin antibody is Dreg 55 or HuDreg 55.

29. A method for treating a patient who has suffered a severe polytraumatic event, comprising administering to said patient a therapeutically effective amount of an anti-L-selectin antibody in a pharmaceutically acceptable carrier to said patient.

30. The method of claim 29, comprising administering a dose of from 1.0 to 10 mg/kg of body weight of said patient to said patient, from 1 to 5 items after suffering said severe polytraumatic event.

31. The method of claim 29, comprising administering a first dose of said anti-L-selectin antibody from 0.5 to 8 hours after said severe polytraumatic event.

32. The method of claim 31, comprising administering said first dose from 0.5 to 4 hours after said severe polytraumatic event.

33. The method of claim 30, comprising administering doses of said anti-L-selectin antibody at intervals of from 6 to 72 hours.

34. The method of claim 33, comprising administering doses of said anti-L-selectin at intervals of from 6 to 36 hours.

35. The method of claim 29, comprising administering said anti-L-selectin antibody up to 10 days after said severe polytraumatic event.

36. The method of claim 35, comprising determining concentration and timing of administration of doses of said anti-L-selectin antibody by determining concentration of anti-L-selectin antibody in serum or plasma of said patient 6-24 hours after administration of a prior dose of said anti-L-selectin antibody.

37. The method of claim 36, wherein a dose of up to 10 mg/kg is administered to a patient in whose serum or plasma concentration of anti-L-selectin antibody is less than 10 μg/ml.

38. The method of claim 36, wherein a dose which is half of a prior dose of anti-L-selectin antibody is administered to a patient in whose serum of plasma concentration of anti-L-selectin antibody is between 10 μg/ml and 50 μg/ml.

39. The method of claim 29, wherein said anti-L-selectin antibody is a humanized antibody.

40. The method of claim 39, wherein said humanized antibody is HuDreg55 or HuDreg200, wherein antibody HuDreg55 comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:2 and a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO:4, and antibody HuDreg200 comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:5 and a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO:6.

41. A method for preventing acute organ damage associated with extracorporeal circulation of a patient's blood through a heart-lung machine, comprising contacting said patient's blood when it is circulating through said heart-lung machine with a pharmaceutical composition with

and anti-L-selectin antibody in a pharmaceutically acceptable carrier 1-30 minutes prior to terminating extracorporeal circulation through said heart-lung machine, at a dose of 1.0 – 10 mg/kg of body weight of said patient.

42. The method of claim 41, wherein said dose contains from 2.0 – 4.0 mg/kg of body weight of said patient.

43. The method of claim 41, wherein said anti-L-selectin antibody is humanized monoclonal antibody.

44. The method of claim 41, wherein said anti-L-selectin antibody is HuDreg200 or HuDreg55, wherein antibody HuDreg55 comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:2 and a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO:4, and antibody HuDreg200 comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:5 and a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO:6.

45. The method of claim 41, further comprising administering 1-3 doses of anti-L-selectin antibody to said patient, each of said doses containing 1-4 mg/kg of body weight of said patient.